

**REMARKS**

**Amendments to the Claims**

Applicants have amended claim 19 to delete the expression “wherein the plurality comprises two or more subsets of cells.”

Applicants have amended claims 19 and 121 to refer to a step of isolating, in a single application, cells that exhibit at least one selected level of fluorescence at a selected wavelength. Support for this amendment may be found, *inter alia*, in paragraphs [0131], [0140], and [0144] of the specification as originally filed.

Applicants have further amended claim 121 to refer to a method of isolating cells each expressing RNAs from two or more RNA expression libraries, thereby improving its form.

Applicants have amended claim 125 to replace the expression “using the selection marker” with the expression “utilizing the selection marker,” thereby improving its form.

Applicants have amended claim 129 and have amended withdrawn claim 110 to improve their form. Further, applicants have amended withdrawn claim 142 to delete the expression “lethal.”

Applicants expressly reserve the right to pursue any canceled or deleted subject matter in subsequent applications that claim benefit from this application.

None of the above amendments adds new matter. Their entry is respectfully requested. Upon entry of the amendments, claims 19, 21, 25, 34, 46, 49, 50, 103, 109, 110, 114, and 117-145 will be pending in this application, with claims 46, 49, 50, 103, 109, 110, 114, 128, and 131-144 having been withdrawn from initial consideration.

**Priority**

According to the Examiner, U.S. Provisional Patent Application No. 60/546,075 (“the ‘075 application”) does not refer to shRNA and thus does not provide adequate support or enablement for any claims referring to shRNA. The Examiner concludes that any claims referring to shRNA have a priority date of February 17, 2005, rather than being entitled to the February 18, 2004 filing date of the ‘075 application.

Applicants direct the Examiner’s attention to p. 69, lines 5-6 of the ‘075 application, which refers to “short RNAs which form stem-loop structures that have an activity similar to siRNA.” Because this section of the ‘075 application clearly describes shRNA, any claims referring to shRNA are entitled to a priority date of February 18, 2004.

**Rejections under 35 U.S.C. § 112, 1<sup>st</sup> Paragraph – Written Description**

Claims 19, 21, 25, 34, 117-120, 122-127, 129, and 145 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. According to the Examiner, the expression “wherein the plurality comprises two or more subsets of cells” in claim 19 is not supported by the specification as originally filed. The Examiner further contends that applicants’ September 2, 2011 Response to the May 5, 2011 Office Action fails to identify support for the amendment adding this expression to claim 19.

Applicants note that the addition of the expression “wherein the plurality comprises two or more subsets of cells” merely improves the form of claim 19, as indicated on p. 18, lines 20-21 of applicants’ September 2, 2011 Response. Because claim 19 refers to a subset of the isolated cells that “expresses an RNA that is not expressed by another subset of the cells,” i.e., a subset that expresses the RNA and a subset that does not, the plurality of isolated cells must comprise two or more subsets by definition. Nevertheless, merely to expedite prosecution,

applicants have amended claim 19 to delete the expression “wherein the plurality comprises two or more subsets of cells” as redundant. Removal of this phrase does not change the scope of the claim. Accordingly, claim 19 as amended, and claims 21, 25, 34, 117-120, 122-127, 129, and 145 dependent therefrom, do not lack written description. Applicants respectfully request reconsideration and withdrawal of this rejection.

**Rejections under 35 U.S.C. § 112, 2<sup>nd</sup> Paragraph -- Indefiniteness**

Claim 145 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner contends that a cell cannot be isolated by the method of claim 145 if the recited RNA or protein is lethal.

Claim 145 refers to a method of isolating a plurality of cells comprising a plurality of DNAs that encode (1) a first RNA and a same nucleic acid tag sequence, and (2) a second RNA under the control of a conditional promoter. According to the method of claim 145, the cells are isolated based on hybridization of a molecular beacon to the nucleic acid tag sequence. At no point does claim 145 refer to, or require, a step of inducing expression of the lethal or damaging second RNA or protein from the conditional promoter. Accordingly, a cell clearly can be isolated by the method of claim 145 regardless of whether the second RNA or a protein encoded by the second RNA is lethal or damaging. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 125 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for being an “improper use claim” under MPEP § 2173.05(q) (Office Action, p. 5). The Examiner suggests rewording claim 125 to recite “utilizing the selection marker after introducing the DNA into the cells but prior to exposing said cells to the signaling probe.”

Applicants have amended claim 125 according to the Examiner's suggestion, thereby obviating this rejection.

**Rejections under 35 U.S.C. § 102 -- Anticipation**

Claims 19, 21, 25, 34, 117-127, 129, and 145 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by U.S. Patent No. 6,692,965 ("Shekdar"). According to the Examiner, Shekdar refers to methods comprising introducing into cells at least one DNA encoding at least one antisense RNA or mRNA and at least one epitope tag, thereby anticipating the claimed methods comprising introducing into cells a plurality of DNAs encoding a plurality of different RNAs, wherein each DNA further encodes a same nucleic acid tag sequence. The Examiner contends that the subject claims encompass the isolation of not only pluralities of cells that encode different RNAs associated with the same nucleic acid tag sequence, but also pluralities of cells that encode the same RNA associated with the same nucleic acid tag sequence, as allegedly referred to in Shekdar.

Claims 19 and 121, and claims 21, 25, 34, 117-120, 122-127, 129, and 145 dependent therefrom, refer to a method of isolating a plurality of cells, wherein a subset of the cells expresses an RNA that is not expressed by another subset of the cells (i.e., the isolated plurality comprises cells expressing different RNAs). Further, all of the cells in the plurality are isolated based on hybridization of a signaling probe to a same nucleic acid tag sequence. Accordingly, in contrast to Shekdar, claims 19, 21, 25, 34, 117-127, 129, and 145 refer to methods of isolating pluralities of cells encoding different RNAs associated with a same nucleic acid tag sequence.

Further, without conceding the correctness of this rejection, but to expedite prosecution, applicants have amended claims 19 and 121 to recite a method of isolating a

plurality of cells in a single application. Shekdar states in column 14, lines 13-23 (emphasis added):

... only a small number of molecular beacons, corresponding to the number of different epitope tags, is needed to prepare a large number of different cell lines expressing one or more proteins. As the fluorescence sorter technology is now limited to three fluorophores, only three different beacons are necessary of this method. Should the technology later allow increased numbers of fluorophores to be detected simultaneously, this may be increased. **However, up to three introduced proteins at one time can be added, then the cells successfully transfected with the three genes can be used as the starting point for the addition of further genes.**

Further, according to column 15, lines 29-31 of Shekdar (emphasis added):

... the advantage to the epitope tag detection method is that separate beacons to each antisense RNA do not have to be made; beacons are needed to only a few epitope tags, which can be used **in successive steps** to introduce a large number of antisense molecules, or over expression of one molecule into a cell line.

Shekdar thus refers to the use of each molecular beacon/nucleic acid tag pair to detect expression of one RNA in each application of the method referred to therein. The claims, as amended, on the other hand, recite the use of the same molecular beacon/nucleic acid tag pair to detect a plurality of different RNAs at the same time.

Claims 19 and 121, and claims 21, 25, 34, 117-120, 122-127, 129, and 145 dependent therefrom, are thus novel over Shekdar.

Claims 19, 21, 25, 117-120, 122-127, 129, and 145 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Publication No. 2003/0215798 (“Short”).

According to the Examiner:

... Short et al. teach utilizing FACS® for DNA recovery, hybridization to a probe of interest, utilizing labels including complementary homopolymeric oligonucleotides, and *in vivo* biopanning methods utilizing molecular beacons. (Office Action, pp. 9-10.)

According to paragraph [0089] of Short, the referenced “labels including complementary homopolymeric oligonucleotides” are used to mark probe DNA, not target RNA. Short thus does not refer to the isolation of a plurality of cells expressing different RNAs based on the hybridization of a molecular beacon to a nucleic acid tag or label shared by the different RNAs.

Further, without conceding the correctness of this rejection, but merely to expedite prosecution, applicants have amended claim 19 to indicate that the cells of the plurality are isolated based on exhibition of at least one selected level of fluorescence at a selected wavelength. The claimed methods thus allow for the isolation of cells expressing different RNAs at a comparable level, based on the detection of a certain level of fluorescence resulting from hybridization of a same molecular beacon to a same nucleic acid tag sequence across the plurality of cells. Nowhere does Short teach or suggest the isolation of a plurality of cells using such parameters. Accordingly, Short does not disclose each and every limitation of claim 19 and claims 21, 25, 117-120, 122-127, 129, and 145 dependent therefrom.

For all of the above reasons, claims 19, 21, 25, 117-120, 122-127, 129, and 145 are not anticipated by Short.

Applicants respectfully request reconsideration and withdrawal of these rejections.

#### **Nonstatutory Obviousness-Type Double Patenting Rejection**

Claims 19, 21, 25, 34, 117-127, 129, and 145 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly obvious over claims 1-33 of Shekdar. Applicants note that, pursuant to 37 C.F.R. § 1.130(a)(1), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an obviousness-

type double patenting rejection. Applicants submit herewith a terminal disclaimer over Shekdar, thereby obviating this rejection.

Claims 19, 21, 25, 34, 117-127, 129 and 145 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly obvious over claims 1-43 of copending U.S. Patent Application No. 12/771,223 (“the ‘223 application”).

According to MPEP § 1504.06:

If a provisional double patenting rejection (of any type) is the only rejection remaining in two conflicting applications, the examiner should withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent.

*See also* MPEP § 804(I)(B)(1):

If a “provisional” nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. . . If “provisional” ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.

The subject application was filed on September 8, 2008, and thus has an earlier filing date than the ‘223 application, which was filed on April 30, 2010. Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection if it becomes the only rejection remaining in the subject case.

**CONCLUSION**

Applicants request favorable consideration of the application as amended and early allowance of the pending claims. To that end, the Examiner is invited to telephone the undersigned to discuss any issue pertaining to this reply.

Respectfully submitted,

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